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EXAMINER
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ART UNIT	PAPER NUMBER
1615	11

DATE MAILED: 08/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/928,466	Applicant(s) SEN ET AL.	
	Examiner Lakshmi S Channavajjala	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of request for extension of time and response dated 5-8-03 is acknowledged.

Status of Claims

Claims 1-63 are pending.

Claim 1 is directed to a fast disintegrating oral composition containing a core made of cefuroxime, an inner sustained release coating of aqueous dispersion of acrylate and methacrylate pH independent, neutral copolymers having quaternary ammonium groups and an outer coating of enteric methacrylic and methacrylic acid esters.

Claims 3-5 recite amounts of cefuroxime.

Claim 6 requires amorphous cefuroxime.

Claims 7- 22 and 48-57 require different percentages, different ratios and molecular weights of inner and outer coating materials.

Claims 2 and 23 recite probenecid, as additional ingredient in the composition.

Claims 24-27 recite diluent, in particular microcrystalline cellulose.

Claims 28-29 recite a wetting agent, claims 30-31, a lubricant; claims 32-33, a disintegrant; claims 34-35, a binder; and claims 36-39, a plasticizer.

Claims 40-47 and 58-63 recite a process of preparing the composition of claim 1, by spraying onto a fluidized bed of cefuroxime core, the polymers of claim 1.

Claim Rejections - 35 USC § 103

Claims 1, 3-22 and 24-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/44614 (hereafter WO) in view of US 5,580,578 to Oshlack et al (hereafter '578).

WO amorphous cefuroxime axetil, a broad-spectrum antibiotic, containing pharmaceutical compositions that are stable during storage period, in the form of tablets, capsules powders etc. WO teaches that amorphous cefuroxime axetil, avoids the disadvantages of being hydrolyzed by esterases (page 1); but has a bitter taste. WO further teaches that film-coating techniques used to mask bitter taste results in gelling of cefuroxime thus causing poor absorption of the drug (page 2). As also admitted by applicants WO states that thin film coating using water-soluble polymers does not completely prevent moisture absorption by cefuroxime axetil. In order to remedy the problem of gelling by cefuroxime axetil, WO suggests employing a micro environmental pH adjustor and an anti-gelling agent around the compound (pages 4-5). As a pH adjustor, WO teaches silicon dioxide or its hydrate and suggests mixing of silicon dioxide with cefuroxime axetil prevents gelation (page 7-8). WO also teaches adding disintegrants, to the above compound (page 9). Further, WO teaches coating cefuroxime axetil with a taste masking film, that is acidic in nature because cefuroxime is less hydrolyzed at acidic pH. WO teaches Eudragit L and Eudragit S, as the suitable polymers for film coating (page 10, l 25-30), which are also described in the instant application for outer coating. WO also teaches adding plasticizers and other excipients in the film forming materials (page 11, l 1-9, l21-25).

WO fails to teach the polymer coating b) and the process of preparing the composition, as claimed.

'578 teach controlled relelase formulations having a coating of aqueous dispersions of a hydrophobic aqueous polymer overran active agent containing core, for taste masking, immediate release and stability over prolonged periods (col. 2, l 5-11 and col. 3, l 31-67). '578 teach that the aqueous dispersion comprises acrylic polymer, which is pH independent and which

does not vary the dissolution rate (col. 4, lines 11-23). Among the acrylic polymers that are suitable for controlled relelase coating, '578 describe Eudragit L, Eudragit S (col. 7, lines 35-67; col. 8, lines 1-10; col. 10, lines 5-26). Further, '578 teach including a permeability-enhancing compound, such that the active agent in the core is released a desired diffusion rate. The suitable permeability enhancing polymers described by '578 include acrylic polymer with at least one quaternary ammonium group 9such as Eudragit RS, RL etc) and thus read on the inner coating of the instant claims (col. 8, lines 11-67, col. 9, lines 1-54). Instant specification also describes Eudragit RL, RS as the suitable polymers for inner coating. Thus, '578 teach acrylic polymers that meet the claimed inner and outer coatings. Further, '578 teach incorporating a number of pharmaceutical excipients such as plasticizers (col. 12 and col. 13), fillers, and lubricants (col. 16). '578 teach employing fluidized bed technique for spraying the acrylic polymer coatings on an active agent-containing core (col. 14, lines 21-67), which reads on the instant process. '578 teach incorporating a variety of active agents, including antibiotics (col. 17, line 2).

It would have been obvious for one of an ordinary skill in the art at the time of the instant invention to include a permeability enhancing coating made of aqueous dispersions of Eudragit RL or RS ('578) in the cefuroxime preparation of WO because '578 teaches aqueous dispersions of acrylic polymers act as taste masking, immediate/controlled release agents (Eudragit R and L) and including a permeability enhancing polymer comprising Eudragit RL or RS or mixtures of RL/RS allows the same diffusion rate of the in the gastrointestinal tract, in a pH independent fashion. Accordingly, one of an ordinary skill in the art would expect to achieve a pH independent relelase of the drug, while still being able to relelase in a controlled fashion. Further, '578 suggests that the dissolution profile may be altered for a given drug, by altering the

molecular weights, percentages, ratio of permeability–enhancing agent and the acrylic polymers (col. 10, lines 27-34). Accordingly, optimizing the percentages and/or ratios of the acrylic polymers with an intention to achieve a desired dissolution profile is within the scope of a skilled artisan. Neither '578 nor WO explicitly state the inlet and outlet temperatures during the process of spray drying. However, optimizing the conditions of coating employing n art recognized process (fluidized bed spraying) is deemed to be within the scope of a skilled artisan. Further incorporating disintegrants, lubricants, filler, diluents etc., in cefuroxime containing compositions for their art recognized effect is deemed to obvious for a skilled artisan.

Claims 2 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/44614 and US 5,580,578 as applied to claims 1, 3-22 and 24-63 above, and further in view of US 4,325,960 to Godtfredsen et al ('960).

WO fails to teach probenecid in cefuroxime axetil containing compositions.

'960 teach compounds useful in the treatment of bacterial infections, in particular, pencillanic acid derivatives. These derivatives are powerful against a wide range of beta-lactamases and act in synergy with cephalosporin and penicillin (col. 1- 3). '960 teach combining beta-lactamase inhibitors with probenecid because the latter blocks tubular excretion of beta-lactam antibiotics. Applicants admit that antibiotics are actively eliminated via renal tubular secretion. Therefore, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to add probenecid (as taught by '960), in effective amounts, to cefuroxime axetil composition of WO, containing acrylic polymeric coatings of WO and '578,

with an expectation to inhibit the tubular excretion of cefuroxime and thus prolong the drug levels in the body and thus its bioavailability.

Response to Arguments

Applicant's arguments filed 5-8-03 have been fully considered but they are not persuasive.

Applicants argue that instant composition is directed to a fast disintegrating controlled release form of cefuroxime axetil, which requires neither the silicon dioxide nor its hydrate as a pH adjuster or an anti-gelling agent as proposed by WO. Further, applicants argue that a cured coated substrate of an aqueous dispersion of plasticized water insoluble acrylic polymer for stability on storage is also not used. Applicants also argue that the selective formulation of the instant claims avoid the problems of gelling agent without the need of silicon dioxide and also achieves a stable controlled release without the need for a complex and cost-extensive cure polymer. Applicants' arguments are fully considered and not found persuasive because instant comprising language allows for the presence of silicon dioxide and the polymers of WO and US 5,580,578. Further, applicants have not shown if the presence of the same would adversely affect the instant formulation. Furthermore, applicants themselves state that instant composition is so designed that the gelling of cefuroxime axetil when in contact with aqueous media is overcome at the same time of achieving controlled release (page 6, lines 25-28 and page 7, lines 1-2). Thus, instant invention is also directed to prevention of gelling of cefuroxime. Applicants' state that cited prior art does not in any manner hint at the possibility of avoiding the problem of gelling and storage stability by a selective inner and outer coating. Applicants' arguments are not persuasive because instant claims are directed to a composition, which do not recite the

limitations of stability and gelling. Further, applicants did not argue the prior art teaching of the claimed polymers for controlled release.

Applicants state the only a combination of polymers results in the controlled release and that US 5580578 does not teach the claimed combination. However, US 5580578 teaches adding acrylic polymer with at least one quaternary ammonium group (such as Eudragit RL or RS) to acrylic polymers such as Eudragit L or Eudragit S, to increase permeability and control the release rate. Thus, US 5580578 suggests the claimed combination of polymers for t he same purpose. Accordingly, the claimed controlled release and observed stability is not unexpected from the teachings of cited prior art. In this regard, US 5580578 teaches all the desired features such as taste masking, immediate (fast) release and stability. Accordingly, one of an ordinary skill in the art would have used the polymers of US 5580578 (for their enhanced permeability, taste masking and stability) in the cefuroxime containing composition of WO with an expectation avoid the gelling problems, increase stability, achieve taste masking as well as an immediate release of cefuroxime.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S Channavajjala whose telephone number is 703-308-2438. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-7924 for regular communications and 703-308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Lakshmi S Channavajjala
Examiner
Art Unit 1615

July 31, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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